

This PA will expire on March 4, 2002 unless reissued.

NOVEL APPROACHES TO ENHANCE ANIMAL STEM CELL RESEARCH

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National Center for Research Resources

National Cancer Institute

National Heart, Lung and Blood Institute

National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institute of Child Health and Human Development

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Mental Health

National Institute of Neurological Disorders and Stroke

National Institute on Deafness and Other Communication Disorders

National Institute on Drug Abuse

THIS PA USES THE "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. IT INCLUDES DETAILED MODIFICATIONS TO STANDARD APPLICATION INSTRUCTIONS THAT MUST BE USED WHEN PREPARING APPLICATIONS IN RESPONSE TO THIS PA.

PURPOSE

The purpose of this program announcement (PA) is to encourage the submission of applications for research to enhance stem cells as a model biological system. Research to isolate, characterize and identify totipotent and multipotent stem cells from nonhuman biomedical research animal models, as well as to generate reagents and techniques to characterize and separate those stem cells from other cell types is encouraged. Innovative approaches to the problems of making multipotent stem cells available from a variety of nonhuman sources, and to creating reagents that will identify those stem cells across species and allow for separation of multipotent stem cells from differentiated cell types, will be stressed. Accordingly, the Exploratory/Developmental Grants (R21) and Research Project (R01) grant mechanisms will be used. This program announcement supersedes PA-99-086 issued earlier by the NCRR.

HEALTHY PEOPLE 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA, Novel Approaches to Enhance Stem Cell Research, is related to the priority areas of cancer, heart disease and stroke, diabetes and chronic disability conditions, maternal and infant health, and others. Potential applicants may obtain a copy of "Healthy People 2010" at <http://www.health.gov/healthypeople/>

ELIGIBILITY REQUIREMENTS

Applications may be submitted by foreign and domestic, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as principal investigators.

MECHANISM OF SUPPORT

The Exploratory/Developmental Grants (R21) mechanism and the Research Project (R01) grant mechanism will be used to support projects under this Program Announcement (PA). Under these mechanisms, the applicant will plan, direct and carry out the research program. The proposed project period during which the research will be conducted should adequately reflect the time required to accomplish the stated goals and be consistent with the policy for grant support. However, because the purpose of R21 grants is to help applicants acquire preliminary data for use in preparing traditional Research Project grant (R01) or Resource-Related Research Project grant (R24) applications, support for the R21 grants is limited to two years with a maximum of \$100,000 direct costs requested per year.

For R01 grant applications, applicants planning to submit an investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended/revised version requesting \$500,000 or more in direct costs for any year are advised that they must contact the Institute or Center (IC) program staff before submitting the application, i.e., as plans for the study are being developed. Furthermore, the applicant must obtain agreement from the IC staff that the IC will accept the application for consideration for award. Finally, the applicant must identify, in a cover letter sent with the application, the staff member and Institute or Center who agreed to accept assignment of the application. This policy requires an applicant to obtain agreement for acceptance of both any such application and any such subsequent amendment. Refer to the NIH

Guide for Grants and Contracts, March 20, 1998 at <http://grants.nih.gov/grants/guide/notice-files/not98-030.html>.

For applications requesting \$250,000 or less in direct costs, specific application instructions have been modified to reflect "MODULAR GRANT" and "JUST-IN-TIME" streamlining efforts being examined by the NIH. The modular grant concept establishes specific modules in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budgetary information is required under this approach. The just-in-time concept allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, reviewers and Institute staff. Complete and detailed instructions and information on Modular Grants can be found at <http://grants.nih.gov/grants/funding/modular/modular.htm>.

RESEARCH OBJECTIVES

Summary

Embryonic stem cells and other stem cells are valuable biomedical research models for the study of biological and disease processes, and for creation of disease models. In addition, these cells hold tremendous promise as model systems for development of therapeutics and for development of replacement tissues through understanding of control of their differentiation.

Thus far, embryonic stem cells have been isolated from several biomedically important nonhuman research models. In addition, stem cells with a more restricted potential have been characterized from post-embryonic tissue types. However, research is needed to provide for a full array of totipotent and multipotent stem cells from nonhuman biomedical research animal models, as well as to provide the research tools to identify, characterize, and purify those cells.

This initiative will support the isolation and characterization of embryonic and other multipotent stem cells in a variety of nonhuman animal species. Examples of research areas appropriate to this announcement include, but are not limited to:

- o Projects to expand the number of nonhuman animal model systems in which embryonic stem cells are available.
- o Projects to identify, isolate, culture and characterize multipotent stem cell populations derived from nonhuman embryonic stem cells.

- o Projects to identify, isolate, culture and characterize multipotent stem cells from post-fetal tissue types.
- o Projects to generate and use panels of markers for stem cell attributes common across species for use in characterization and isolation of stem cells in a range of animal species or tissues
- o Projects to create universal methods of culture to maintain the undifferentiated state of embryonic or other characterized, multipotential stem cells across nonhuman animal species.

Projects supported by the National Center for Research Resources under this PA are intended to generate research tools, reagents or multipotential stem cells of utility to research on a broad range of tissue or cell types and of interest to more than one categorical or disease-oriented Institute or Center of the National Institutes of Health. Projects that will focus on research on tissues or disease processes specific to the mission of an Institute or Center should be directed to the respective Institute or Center.

The research supported under this PA should clearly expand the usefulness of nonhuman animal model systems by generating multipotential stem cells appropriate to those systems and tools that will allow for further research on those stem cells. The results of R21 projects are expected to include preliminary data appropriate for applications for further support through the Research Project grant (R01) or Resource-Related Research Projects grant (R24) mechanism.

URLS IN NIH GRANT APPLICATIONS OR APPENDICES

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Reviewers are cautioned that their anonymity may be compromised when they directly access an Internet site.

APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (rev. 4/98) and will be accepted at the standard application deadlines as indicated in the application kit. Application kits are available at most institutional offices of sponsored research and may be obtained from the:

Division of Extramural Outreach and Information Resources
National Institutes of Health
6701 Rockledge Drive, MSC 7910
Bethesda, MD 20892-7910
Telephone 301-435-0714
E-mail: grantsinfo@nih.gov.

Forms are online at:
<http://grants.nih.gov/grants/funding/phs398/phs398.html>.

The title and number of the announcement must be typed in Section 2a on the face page of all applications.

o FACE PAGE: Items 7a and 7b should be completed, indicating Direct Costs (in \$25,000 increments up to a maximum of \$250,000) and Total Costs [Modular Total Direct plus Facilities and Administrative (F&A) costs] for the initial budget period. (Applications that request more than \$250,000 direct costs in any year must follow the traditional PHS 398 application instructions.) Items 8a and 8b should be completed indicating the Direct and Total Costs for the entire proposed period of support.

o DETAILED BUDGET FOR THE INITIAL BUDGET PERIOD - Do not complete Form Page 4 of the PHS 398. It is not required and will not be accepted with the application.

o BUDGET FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT - Do not complete the categorical budget table on Form Page 5 of the PHS 398. It is not required and will not be accepted with the application.

o NARRATIVE BUDGET JUSTIFICATION - Use a Modular Grant Budget Narrative page. (See <http://grants.nih.gov/grants/funding/modular/modular.htm> for sample pages.) At the top of the page, enter the total direct costs requested for each year.

o Under Personnel, List all project personnel, including their names, percent of effort, and roles on the project. No individual salary information should be provided.

o For Consortium/Contractual costs, provide an estimate of total costs (direct plus facilities and administrative) for each year, each rounded to the nearest \$1,000. List the individuals/organizations with whom consortium or contractual arrangements have been made,

the percent effort of all personnel, and the role on the project. Indicate whether the collaborating institution is foreign or domestic. The total cost for a consortium/contractual arrangement is included in the overall requested modular direct cost amount.

o Provide an additional narrative budget justification for any variation in the number of modules requested.

o BIOGRAPHICAL SKETCH - The Biographical Sketch provides information used by reviewers in the assessment of each individual's qualifications for a specific role in the proposed project, as well as to evaluate the overall qualifications of the research team. A biographical sketch is required for key personnel, following the instructions below. No more than three pages may be used for each person. A sample biographical sketch may be viewed at:

<http://grants.nih.gov/grants/funding/modular/modular.htm>.

-Complete the educational block at the top of the form page;

-List current position(s) and then previous positions;

-List selected peer-reviewed publications, with full citations;

-Provide information, including overall goals and responsibilities, on research projects ongoing or completed during the last three years.

o CHECKLIST - This page should be completed and submitted with the application. If the F&A rate agreement has been established, indicate the type of agreement and the date. It is important to identify all exclusions that were used in the calculation of the F&A costs for the initial budget period and all future budget years.

For all applications, the completed original application and five legible copies must be sent or delivered to:

CENTER FOR SCIENTIFIC REVIEW (formerly Division of Research Grants)

NATIONAL INSTITUTES OF HEALTH

6701 ROCKLEDGE DRIVE, ROOM 1040-MSC 7710

BETHESDA, MD 20892-7710

BETHESDA, MD 20817 (for express/courier service)

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established Public Health Service referral guidelines and applications will be reviewed for completeness by the Center for Scientific Review (CRS). Applications will be reviewed for scientific and technical merit in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and may undergo a process in which only those applications deemed to have the highest scientific merit, generally the top one half of applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

- o Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?
- o Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?
- o Innovation: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?
- o Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

- o Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

Innovation and potential significance of the proposed research are major considerations in the evaluation of applications for R21 grants.

In addition to the above criteria, in accordance with NIH policy, all applications will be reviewed with respect to the following:

- o Appropriateness of the proposed budget and duration in relation to the proposed research.
- o The adequacy of the proposed protection for animals or the environment, to the extent they may be adversely affected by the project proposed in the application.

AWARD CRITERIA

Applications will compete for available funds with all other recommended applications assigned to that Institute or Center. The following will be considered in making funding decisions:

- o Quality of the proposed project as determined by peer review
- o Availability of funds
- o Program priority.

INQUIRIES

Inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

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Direct inquiries regarding fiscal matters to:

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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Nos. 93.306, 93.396, 93.839, 93.846, 93.864, 93.849, 93.242, 93.853, 93.173, 93.279. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under NIH grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74 or 92. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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